UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/336,672	06/17/99	HERRATH M	SCRIP1100

HM12/0717
GRAY CARY WARE & FREIDENRICH LLP
4365 EXECUTIVE DRIVE
SUITE 1600
SAN DIEGO CA 92121-2189

EXAMINER	
SANDALS,W	
ART UNIT	PAPER NUMBER
1636	19

DATE MAILED: 07/17/01

Please find below and/or attached an Office communication concerning this application or pr ceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/336,672	Applicant(s) Von Herrath
	Examiner WILLIAM SANDALS	Art Unit 1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 26, 2001*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-3, 5, 7-14, 16-24, and 26-39* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 5, 7-14, 16-24, and 26-39* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *11*
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. The request filed on April 26, 2001 in Paper No. 17 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/366,672 is acceptable and a CPA has been established. An action on the CPA follows.

Response to Amendment

2. The declaration under 37 CFR 1.132 filed April 26, 2001 is insufficient to overcome the rejection of claims 1-3, 5, 7-14, 16-24 and 26-39 based upon lack of enablement under 35 USC 112, first paragraph as set forth in the last Office action because: The Declaration is unsigned.

Response to Arguments

3. Arguments filed in Paper No. 18, filed April 26, 2001 regarding the rejection of claims 1-3, 5, 7-14, 16-24 and 26-39 under 35 USC under 35 USC 112, first paragraph have been fully considered but they are not persuasive. The response to the arguments is contained in the rejection repeated below.

4. Applicant's amendments to the claims in Paper No.18 have overcome the rejection of claims 7-9, 17, 20, 29, 30 and 36 under 35 USC 112, second paragraph in the previous office action, and the rejection is withdrawn. New grounds for rejection under 112, second paragraph appear below.

5. Applicant's amendments to the specification in Paper No. 18 have overcome the objection to the specification in the previous office action, and the objection is withdrawn.

6. Paper No. 18 states that claim 4 is under consideration. Claim 4 was cancelled in Paper No. 12, filed December 28, 2000.

7. New grounds of rejection appear below.

Claim Objections

8. Claims 8 and 29 are objected to because of the following informalities: claim 8 depends from cancelled claim 6, and claim 29, at line 3, the bracket on the right side of "IL-10" is facing in the leftward direction, it should be facing in the rightward direction to indicate the deletion of material to the right of "IL-10". Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. Claims 1-3, 5, 7-14, 16-24 and 26-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition and method for treatment of diabetes in a mouse model system, does not reasonably provide enablement for treatment of any autoimmune disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to a composition and method for treating or preventing an autoimmune disorder by administering a nucleic acid construct encoding at least one epitope from a self-antigen to an animal. While applicants have shown a method of treatment of diabetes in a mouse model system, they have not demonstrated a method of treatment of **any** autoimmune disorder. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve a development of a method of treatment for each autoimmune disorder.

b- Guidance is provided which demonstrates a treatment of a mouse model system for diabetes, along with experimental data for the treatment of diabetes in a mouse model system. Only prophetic guidance is provided for other autoimmune disorders.

c- The nature of the invention is complex. Treatment or prevention of diabetes by gene therapy is still in a developmental stage, and as such is highly unpredictable.

d- The prior art has taught the gene therapeutic treatment of diabetes with replacement of cells which will produce insulin. Induction of immunologic anergy toward insulin producing cells has only been prophetically taught as described in Giannoukakis et al. at page 2107, column 2, where they state "[i]ntervention aimed at limiting islet damage will become plausible only

when more satisfactory risk prediction protocols are developed. However, some safe preventive measures have already been explored in animal models and may eventually be applied to humans."

e- Giannoukakis et al. have taught the unpredictability of the claimed invention at page 2117 column 2 where they state "[a] better understanding of the genetics, the environmental triggers, and the immunopathology of type I diabetes, together with the factors affecting islet engraftment, as well as allogeneic and xenogeneic tolerance and protection from immune destruction, is necessary for these approaches to find clinical use."

f- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

Response to Arguments

10. Arguments presented in Paper No. 7 assert that the rejection is based on "safety issues". The rejection is based upon the teachings of lack of enablement in the prior art. The quoted sections from Giannoukakis et al. above state very clearly that the animal models have not been established as predictive, and that the understanding of the immunology of tolerance is still poorly understood. This being the case, the burden is high upon the instant inventors to provide all of the necessary teachings for enablement of the invention. Therefore, the instant claims and specification do not provide enablement for the full scope of the claims as written.

11. Paper No 7. also asserts that the specification provides support for the use of animal models. The cited paragraph is general and provides support for the concept that an antigenic epitope recognized by the immune system of a species may also be recognized by the immune system of another species. Teachings on the reactivity of an epitope in more than one species, does not provide teachings on how to practice immune suppression of an autoimmune disease.

12. Arguments set forth in Paper No. 18 assert that the fact pattern of Giannoukakis does not apply to the instant claimed invention. Giannoukakis discusses the limited knowledge of those of skill in the art of how to use gene therapy to modulate an immune response to diabetes, as discussed above. This discussion is very pertinent, since Giannoukakis article was published subsequent to the filing date of the instant application. Giannoukakis taught that gene therapy for the treatment of diabetes was a poorly understood art.

13. Arguments set forth in Paper No. 18 assert that the mouse models cited are predictive models for human diabetes. No such evidence has been presented. The article by Delovitch et al. submitted with Paper No. 18 is presented in support of the position that the mouse models are predictive of diabetes in humans. Delovitch et al. state in the introduction "experiments conducted with NOD mice in recent years have begun to provide clues about how we may modulate and regulate the immune response in order to protect against IDDM in humans". This statement makes it clear that the mouse model is still being developed. Therefore, the results of the mouse model is not convincing as evidence of a full scope of enablement.

14. Discussion of the Declaration of Dr. von Herrath of Paper No. 13, filed December 28, 2000 were made of record in the Advisory Action mailed January 12, 2001. Arguments set forth in Paper No. 18 state that difference in the values for controls in Figure 2 of the Declaration of Paper No. 13 are because the controls "were not the same" for each experiment. This being the case, the data are not comparable, and the value of the data presented in Figure 2 of the Declaration of Paper No. 13 is not interpretable, and therefore the data is not convincing.

15. Arguments set forth in Paper No. 18 assert that the data of the unsigned Declaration of Dr. von Herrath controverts the assertion of that Table 2 shows that only IL-4 provided any benefit in the claimed method. These arguments will be addressed at such time as a signed declaration is entered.

16. The conclusion stated in the Advisory Action regarding the limitation of the claims to enablement for IL-4 only, is sustained. The data presented in the Declaration of Paper No. 13 make it clear that only IL-4 may have any effect in modulating the immune response. INF-gamma was shown to produce a negative effect, teaching away from the claimed method. The showing of this data is convincing that of the many cytokines used in the experiments of the Declaration of Paper No. 13, only IL-4 had any possible effect on the instant claimed method. Therefore, given these facts, the claims to cytokine, chemokine, interferon, and ligands for lymphocyte receptors are held to be non-enabled. Claims to IL-4 and IL-10 will be subject to further review should the unsigned Declaration of Dr. von Herrath be signed and entered.

17. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claims 1-3, 5, 7-10, 14, 20, 21, 24, 31, 34 and 37-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

19. Claim 1, lines 2-3 recites "comprising a nucleic acid construct encoding at least one epitope from a self-antigen and a compound selected from the group consisting of". It is not clear from this language if the "compound" is encoded by the plasmid, or not. Since the language is unclear, the claim is vague and indefinite. For the purposes of examination, it is assumed that the "compound" is not encoded by the nucleic acid.

20. Claim 8 recites the limitation "the biological response modifier" in line 1. There is insufficient antecedent basis for this limitation in the claim.

21. Claims 8 and 28 recite the limitation "biological response modifier". "Biological response modifier" is not an art recognized term, and no definition is provided in the claims and specification to inform one of skill in the art exactly what is meant by this term. As a result the claim is vague and indefinite.

22. Claims 9 recites at line 3 that the construct comprises the at least one epitope **or** (emphasis added) the compound. The base claim 1 recites that the construct comprises the at

least one epitope. The meaning of the word "or" in this claim makes the meaning of claim 1 unclear, since the construct may now **not** include the at least one epitope.

23. Claims 10, 21 and 31 recite a list of promoters. Some of the "promoters" are listed simply as (for example) "Moloney virus", without stating that the entity being claimed is indeed a promoter. As a result, it is not clear that the entities which do not state "promoter" are indeed meant to be promoters.

24. Claims 14, 24 and 37-39 recite the limitation "derived from". One of ordinary skill in the art would not know how to interpret the metes and bounds of this limitation. A derivation of an epitope may be closely patterned after the subject epitope or may be very loosely patterned after the subject epitope, such that it may bear no resemblance or form recognizable as the subject epitope which may be chemically and/or biologically totally unrelated in function or form to the subject epitope.

25. Claims 20 recites at line 3 that the construct comprises the at least one epitope **or** (emphasis added) the compound. The base claim 11 recites that the construct comprises the at least one epitope. The meaning of the word "or" in this claim makes the meaning of claim 1 unclear, since the construct may now **not** include the at least one epitope.

26. Claim 34 recites at lines 1-2 "the immune response affects T-cells". No definition of the term "affects" is provided in the claims or specification. This term is not an art recognized term, and as such the claim is vague and indefinite.

Claim Rejections - 35 USC § 102

27. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

28. Claims 1, 2, 5 and 7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 97/46253.

WO 97/46253 taught (see especially the abstract, the summary, pages 22 and 23) an immunomodulating composition comprising a nucleic acid construct (plasmid) encoding at least one epitope from a self-antigen and a gene encoding a cytokine (IL-4, IL-10).

Claim Rejections - 35 USC § 103

29. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

30. Claims 1-3, 5, 7-14, 16-24 and 26-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. in view of WO 97/46253.

The invention is also drawn to an immunomodulating composition comprising a nucleic acid construct (plasmid) encoding at least one epitope from a self-antigen and a cytokine. The

epitope was an antigen associated with diabetes. The plasmid comprised a promoter. Also claimed is a method of modifying an ongoing immune response to a self-antigen of autoimmune diabetes by administering the self antigen to an animal to produce a positive regulatory immune response associated with autoimmune diabetes, and to control blood glucose levels.

Liu et al. taught (see especially the abstract, materials and methods and page 202, column 2, last paragraph) an immunomodulating composition comprising a nucleic acid construct (plasmid) encoding at least one epitope from a self-antigen (GAD65) and a cytokine. The epitope was an antigen associated with diabetes. The plasmid comprised the CMV promoter. that the administration of GAD65 to a NOD mouse caused the reduction of insulitis. Liu et al. teaches at page 202, column 2 that the administration of cytokines is known to delay the onset of diabetes, and states that the combined injection of a DNA encoding a self-antigen and a DNA encoding a cytokine would produce a therapeutic benefit.

Liu et al. did not teach that the method produced control of blood glucose levels and suggested the combination of a DNA encoding a self-antigen and a DNA encoding a cytokine would produce a therapeutic benefit.

WO 97/46253 teaches at page 12, the introduction of a gene encoding a self-antigen to produce a therapeutic result in an autoimmune disease, and at page 22 teaches the co-introduction of a gene encoding IL-4 and IL-10 to stimulate, modify or modulate a host's immune response. At page 21, diabetes is listed as an autoimmune disease which may be treated by the administration of the gene encoding a self-antigen and the gene encoding IL-4 and IL-10. At

page 18, WO 97/46253 teaches that the method may produce a switch from a "'Th1' to a 'Th1' response". WO 97/46253 discusses the relationship of insulitis to blood sugar levels at pages 10-12.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant application to combine the composition and method of treating autoimmune diabetes insulitis with a gene encoding a self-antigen of Liu et al. with the composition and method of treating autoimmune diabetes and a gene encoding a cytokine of WO 97/46253 because they were both treating autoimmune diabetes with self-antigen immunotherapy.

One of ordinary skill in the art would have been motivated to combine the teachings of Liu et al. with WO 97/46253 because Liu et al. taught the specific self-antigen involved in autoimmune diabetes, suggesting the combination of the self-antigen and a cytokine to improve the immunoregulatory response, and WO 97/46253 taught the co-introduction of a gene encoding a self-antigen and the gene encoding IL-4 and IL-10 to stimulate, modify or modulate a host's immune response in the control of autoimmune diabetes. The teachings of both Liu et al. and WO 97/46253 are directed to control of autoimmune diabetes insulitis. WO 97/46253 taught that the control of autoimmune diabetes would obviously include control of a major symptom of autoimmune diabetes, namely, the control of blood sugar (glucose) levels. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Liu et al. with WO 97/46253.

Conclusion

31. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Richard Schwartz can be reached at (703) 308-1133.

Any inquiry of a general nature or relating to the status of this application should be directed to the Zeta Adams, whose telephone number is (703) 305-3291.

William Sandals, Ph.D.
Examiner
July 15, 2001

TERRY MCKELVEY
PRIMARY EXAMINER